REMARKS

This is being filed in response to the Official Action dated October 14, 2005. The claims currently pending and under examination are claims 1, 10-15 and 31. A request for a three month extension of time accompanies this response. Favorable consideration and allowance of this application are respectfully requested in view of the following remarks.

The Applicants wish to thank the Examiner for the helpful telephonic discussion with the undersigned which took place on February 13, 2006, in which the known homology among RNA polymerases was discussed. It was suggested that claim amendments be made to incorporate more specific teachings of the modifications described in the specification that increase the fidelity of the polymerase.

Applicants herein amend Claim 1 to incorporate the specific substitutions in the RNA-dependent RNA polymerase that are described in the specification on pages 13-15. Applicants have made the amendment to expedite prosecution of the Application, but expressly reserve the right to pursue the original claims in a further continuation application. No new matter is added.

The Office Action rejects Claims 1, 10-15 and 31 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the Written Description Requirement. Applicants respectfully disagree.

The Examiner states that there is not a well-established relationship between polymerase structure and fidelity in the coxsackievirus art or a well-established relationship between attenuation and the full spectrum of possible alterations to the coxsackievirus genome. As support, the Examiner cites Jablonski *et al.* (1991) *J. Virol.* 4564-4572 ("Jablonski"). The Office Action also alleges that there is no species of the claimed invention that is reduced to practice and no demonstration of the increased fidelity.

First, it must be remembered that "[t]he purpose of the adequate written description requirement is to ensure that the inventor had possession of the claimed subject matter at the time the application was filed. If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate

written description requirement is met." *In re Alton,* 76 F.3d 1168, 1175, 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996).

Further, there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed (see Federal Register, Vol. 66, No. 4 (January 5, 2001) page 1105, column 1 (citing *In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90, 97 (CCPA 1976))). In cases in which the claims are drawn to a genus, it must be determined whether the art indicates that there is substantial variation among the species within the genus of the claimed subject matter (see Revised Interim Written Description Guidelines Training Materials). The Examiner should then determine whether a representative number of species is *implicitly or explicitly* disclosed (note that actual examples are not a requirement)(see Revised Interim Written Description Guidelines Training Materials). A representative number of species depends on whether one of skill in the art would recognize that the Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed (Federal Register, Vol. 66, No. 4 (January 5, 2001) page 1106, column 3). No actual example is required in order to satisfy the Written Description Requirement.

In the present case, the Specification clearly discloses at page 13, lines 28-35 through page 15, lines 1-2, that certain mutations in RDPs (RNA-dependent polymerases) are known to affect the fidelity of the RDPs. For example, codon 328 (glycine) of the 3D RDP may be mutated to serine, cysteines or alanine and are associated with decreased fidelity see page 13, lines 28-35 through page 14, lines 1-9). Conversely, a mutation of this codon to leucine or isoleucine (and mutation of the preceding codon from tyrosine to phenylalanine) is associated with *increased* fidelity of the RDP (see page 14, lines 11-15). Thus, the specification does provide disclosure of mutations associated with increased fidelity.

Further, examples of mutations causing increased fidelity of reverse transcriptase are disclosed for HIV-1 at page 14, lines 16-21.

Further still, the Applicants disclose that mutations in the "finger region" of the HIV-1 polymerase are associated with fidelity of the enzyme. The Applicants state that "[s]imilar mutations introduced into enterovirus RNA polymerases are expected to have a similar effect *due to the close structural and sequence homology among the RDPs* (Specification at page

14, lines 26-29, emphasis added). The Specification then details positions of RDPs that correspond to positions of reverse transcriptases (Specification at page 14, lines 29-34). Thus, the structural features are prominent enough to have corresponding amino acids in the RDPs.

As described in the introduction of O'Reilly and Kao (1998) *Virol.* 252:287-303 (Applicants' IDS, reference BB):

> Kamer and Argos (1984) identified sequence motifs common among the putative RdRps ["RNA-dependent RNA polymerases"] of several animal and plant positive strand RNA viruses and the poliovirus 3D polymerase. Subsequent analyses expanded on these observations with a broader range of viruses and additional motifs. Currently, there are eight conserved RdRp motifs (Koonin, 1991; Poch *et al.* 1989). Four of these eight conserved motifs are now known to be present in all classes of polymerases and reside in the catalytic portion of the "palm" domain (Hansen *et al.*, 1997; Ollis *et al.* 1985). There is a growing body of information available on polymerase structure/function, including the first crystal structure of an RNA-dependent RNA polymerase, the $3D^{pol}$ protein of poliovirus (Hansen *et al.* 1997).

Thus, it had been known in the art that RDPs had common, conserved structural/functional domains.

The Applicants disclose, and the art recognized close structural/functional attributes shared among RDPs and the corresponding related reverse transcriptases. The specification also details the regions of the RDPs related to enzyme fidelity. Therefore, the Specification provides a sufficient nexus between polymerase structure and fidelity with reference to specific examples from the literature of domains of RDP that are associated with fidelity of the enzyme. The Specification also provides an assay for which to perform routine experimentation to identify those structural changes that result in increased fidelity. Therefore, Applicants request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Finally, in order to expedite prosecution of the application, the Applicants have amended claim 1 to incorporate the specific teachings of the specification with regard to the substitutions that can be made in the RNA polymerase to increase fidelity of the enzyme.

In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection set forth in the October 14, 2005 Official Action, and an early allowance of this application.

Respectfully submitted,

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